In This Issue

Cell

The Alter Ego of the Androgen Receptor in Prostate Cancer

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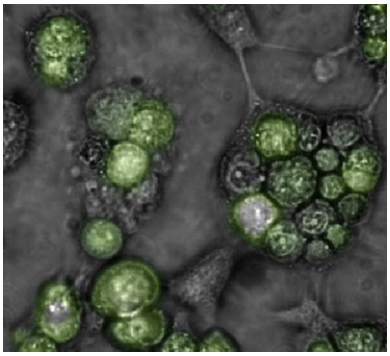
Prostate cancer switches from an androgen-dependent to a more advanced, androgen-independent state. The androgen receptor (AR) plays an essential role in both states. Wang et al. now find that the gene expression program regulated by AR in androgen-dependent cancer cells is very different from the one in androgen-independent cells. Due to differences in chromatin marks in the independent state, AR selectively upregulates genes that promote cancer cell growth, such as cell-cycle regulators. These results show that AR has different functions in androgen-independent tumors and suggest new targets for the treatment of advanced prostate tumors.

Harnessing Phagocytosis for Cancer Therapy



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Hematopoietic stem cells (HSCs) have the ability to mobilize into the circulation and seed peripheral tissues. In doing so, they must cross macrophage-lined sinusoids that guard entry into hematopoietic sites. Jaiswal et al. find that normal migrating HSCs, as well as leukemic stem cells (LSC), upregulate an inhibitor of phagocytosis, CD47. In an accompanying study, Majeti et al. report increased expression of CD47 on human LSCs and demonstrate that CD47 is an adverse prognostic factor in acute myeloid leukemia (AML). Monoclonal antibodies that block CD47 enable phagocytosis of LSC, and treatment of LSC-engrafted mice depletes AML. Together, these studies suggest that hematopoiesis is regulatable by phagocytosis, and that macrophages may play a previously unrecognized role in tumor immunosurveillance. Furthermore, they provide a rationale for using a blocking anti-CD47 antibody as an LSC-targeted AML therapy.

Heart Muscle Cells Divide and Conquer

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Tissue regeneration in metazoans typically involves proliferation and differentiation of undifferentiated stem and progenitor cells. Bersell et al. show that the heart muscle, a tissue that regenerates poorly, can heal itself through proliferation of differentiated heart muscle cells. The authors also report that this process is regulated by the growth factor neuregulin1 and its tyrosine kinase receptor ErbB4. This study may provide the foundation for novel strategies to treat heart failure in human patients.

Cytokine Leaves Little to Chance in HSC Differentiation

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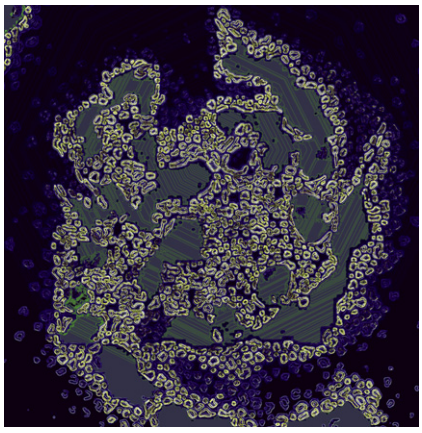
Hematopoietic stem cells (HSCs) differentiate into progenitors of the different blood cell lineages. It has been generally thought that initial HSC lineage choices are stochastic, and that cytokines can then trigger amplification of a particular progenitor type. Sarrazin et al. now show that the cytokine M-CSF can directly instruct myeloid lineage bias in HSC, in an integrated circuit with the transcription factor MafB. At low MafB levels, M-CSF specifically stimulates asymmetric HSC divisions in which one of the daughters acquires myeloid fate. This study suggests that variations in levels of a transcription factor can render cytokine signaling instructive for a specific stem cell fate.



A New Member of the RNA Silencing Ars-enal

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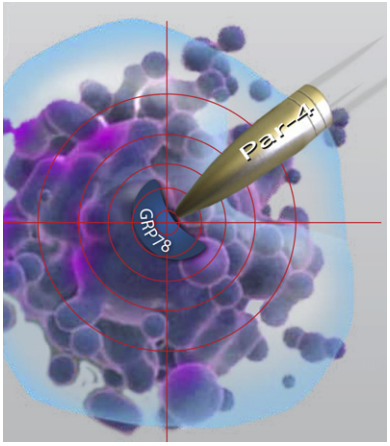
Small RNA silencing pathways control many aspects of biology from cell proliferation to antiviral defense. Two studies identify an unexpected player, Arsenic resistance protein 2 (Ars2), in small RNA biogenesis. Sabin et al. show that Ars2 plays a critical role in miRNA-mediated gene silencing as well as in the antiviral RNAi response in flies. Gruber et al. show that Ars2 is a component of the nuclear RNA cap-binding complex that selectively regulates miRNA-mediated gene silencing in actively dividing mammalian cells, and that it is required for proliferation. Thus Ars2 is an essential component of multiple silencing pathways.

For Par-4, the Apoptosis Party Is BYOR



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The tumor suppressor prostate apoptosis response-4 (Par-4) is a proapoptotic protein with known functions in the cytoplasm and nucleus. Burikhanov et al. now identify an extrinsic pathway for apoptosis induction by Par-4. In response to ER stress, intracellular Par-4 is secreted and transports its own receptor, GRP78, from the ER to the cell surface. Binding of Par-4 to cell surface GRP78 amplifies the ER stress loop, thereby activating apoptosis. Moreover, apoptosis induced by TRAIL, which also exerts cancer cell-specific effects, is dependent on extracellular Par-4 signaling via cell surface GRP78. This extracellular role for Par-4 significantly broadens its therapeutic potential for tumors.

A Triumvirate Drives Transcription Factor Diversification

PAGE 314

In multicellular organisms, specific interactions between transcription factors (TFs) and between TFs and their target genes modulate gene expression. TFs with similar DNA-binding domains form families that can expand by gene duplication and mutation. Grove et al. use a systems approach to examine the full *C. elegans* bHLH family for specific contributors to TF diversification. The resulting network, which integrates TF dimerization interactions, tissue- and cell-specific expression patterns, and DNA-binding specificity, reveals that all three parameters contribute equally to bHLH divergence. This analysis sets the stage for cross-species comparisons of integrated networks that could provide insights into protein family evolution in complex metazoan organisms.

Only Stem Cells Need Their Cyclin A

PAGE 352

The mammalian cell cycle is regulated by kinases and their cyclin regulators. Cyclin A has been considered an essential component of the core cell-cycle engine. Kalaszczynska et al. now demonstrate that ablation of cyclin A in fibroblasts does not affect cell proliferation, and that the functions of cyclin A are carried out by cyclin E. In contrast, cyclin A function is essential for proliferation of hematopoietic and embryonic stem cells. This differential requirement for cyclin A in stem cell compartments reveals cyclin A as a potential target in cancer stem cell-based therapies.

Finding the Positive Side of Microtubules

PAGE 366

Microtubule plus-end tracking proteins (+TIPs) associate with growing microtubule ends and control microtubule interactions with different cellular structures during cell division, migration, and morphogenesis. EB1 and its homologs are highly conserved proteins that play an important role in the targeting of +TIPs to microtubule ends, but the underlying molecular mechanism has been elusive. Using a multidisciplinary approach, Honnappa et al. discover a short polypeptide motif that is used by numerous +TIPs for localization to microtubule tips in an EB1-dependent manner. Their findings establish a general microtubule tip localization signal and delineate a mechanism for this subcellular protein targeting process.

EnCompPASSing Human DUB-Interacting Proteins

PAGE 389

Dynamic regulation of protein abundance and activity can be achieved through post-translational ubiquitination of target proteins. Ubiquitin removal from proteins via deubiquitinating enzymes (DUBs) has recently emerged as an important level of regulation. For most Dubs, however, their functions, targets, and regulation are poorly understood. Combining interaction proteomics with a broadly applicable software platform termed *CompPASS,* Sowa et al. have identified 774 candidate interacting proteins associated with 75 human DUBs. This study provides an initial view of the DUB interaction landscape and links specific DUBs to diverse cellular processes including transcription, RNA processing, DNA damage, and endoplasmic reticulum-associated degradation.